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Preface

Matrix Metalloproteinases

Proteolysis is a fundamental aspect of life, starting from its beginning to its inevitable end. Life, as we know it, will not exist without the action of proteolytic enzymes, which cooperatively contribute to the evolution and survival of all living organisms by altering the cellular proteome. This special issue focuses on recent advances in a major group of proteases, namely the matrix metalloproteinase (MMP) family of zinc-dependent endopeptidases. Although traditionally viewed as extracellular matrix (ECM) degrading proteases, the MMPs hydrolyze multiple proteins at distinct subcellular and cellular sites and thereby influence many biological processes in a highly regulated fashion. Controlled MMP-dependent proteolysis is essential for the normal function of the organism while deregulated MMP activity can lead to development of disease. The importance of MMPs in the pathogenesis of cardiovascular disease, neurological disease and cancer, just to mention a few, is irrefutable. In recent years, there has been an exponential growth in our knowledge of MMP function thanks to various technological advances in structural biology, proteomics, degradomics, and animal models. We have learned that the MMP family is not a monolithic group of proteases but rather is comprised of structurally and functionally distinct proteases, each with its unique spatial and temporal expression, substrate profile, and biological function. Advances in structural biology provided exquisite insight into the structural features of MMP domains and the mechanism of catalysis and inhibition at the atomic level. Proteomic based approaches have considerably expanded the substrate profile of MMPs, revealing unexpected targets and biological functions. Studies with genetically modified mice have revealed new roles for MMPs in development and in various physiological and pathological conditions. We have seen the emergence of new chemical and biological approaches to MMP inhibition and the design of molecular beacons to detect enzymatic activity *in vivo*. Collectively this new and vast information has generated new concepts in MMP biology. It has also helped to explain some of the reasons behind the failure of MMP inhibitors in the clinical trials that were conducted during the 1980s and 1990s with cancer patients. There is no doubt that this knowledge and the lessons learned from the early trials will contribute to the development of novel and better strategies for targeting deregulated MMP activity in disease conditions.

Current research into the function and regulation of MMPs continues to generate new discoveries and also raises more questions. This special issue of BBA-Molecular and Cell Research strives to provide an overview of some of the recent advances in the MMP field in areas as diverse as structure, function, inhibition, and drug development. The goal of these reviews is also to address controversial issues and to serve as a forum to disclose new ideas and concepts on MMP biology. With this in mind, this special issue of BBA-Molecular and Cell Research was assembled with 11 scientific reviews from leading investigators in various aspects of MMP research. This volume begins with a review from Dr. Fanjul-Fernandez and her colleagues, which provides a comprehensive and up-to-date overview of the MMP family. The authors discuss MMP evolution, structure, and regulation with emphasis on MMPs' biological role in human diseases and in mouse transgenic models. A review from Dr. Tallant et al. provides new insights into the structural determinants of the catalytic domains of MMPs and their implication for drug design. Based on new disclosures of MMP structure, allosteric regulation, and substrate interactions, Dr. Sela and colleagues highlight the potential of MMP domains, other than the active site, as new targets for inhibition of enzymatic activity. The importance of defining the substrate profile of MMPs, referred to as degradomics, is the topic of a review by Dr. Rodriguez et al. MMP degradomics continues to be a challenging task, in particular *in vivo*, that is at the core of defining the physiological roles of MMPs. MMP-dependent proteolysis is controlled by the action of their endogenous inhibitors, the tissue inhibitors of metalloproteinases (TIMPs). This special issue includes a comprehensive and up-to-date review by Dr. Brew and Dr. Nagase, which covers new findings on the structural features and biological functions of TIMPs. Two reviews cover distinct aspects of MMP inhibition; inhibitor design and the complexities of targeting MMP activity in cancer as a targeted disease. Dr. Jacobsen et al. discuss the pros and cons of different strategies under development to block the catalytic center of MMPs with chemical inhibitors. Dr. Kruger and his colleagues highlight the need to understand MMP function within the context of proteolytic networks in cancer tissues for achieving productive and therapeutic MMP inhibition. They also discuss the potential consequences of specific vs. broad inhibition of MMP activity for therapeutic efficacy. A review by Dr. Deryugina and Dr. Quigley discusses the complex roles that MMPs play in tumor metastasis and angiogenesis. The authors highlight the diverse and sometimes opposing actions that MMPs may elicit in cancer progression and their potential impact on anti-MMP therapies. The multifaceted biological consequences of metalloproteinase activity as revealed in genetically modified mice is the topic of a review by Dr. Aiken and Dr. Khokha focusing on skeletal tissue, as a model system. This special issue concludes with two reviews focusing on MT1-MMP, a member of the membrane type MMP subfamily. Dr. Alex Strongin's review provides an overview on the structure, function and inhibition of MT1-MMP. It also covers emerging data on the interactions between MT1-MMP and TIMP-2 and the consequences of these interactions for proteolytic and non-proteolytic events. Finally, Dr. Gingras and Dr. Beliveau describe new findings on the role of the cytoplasmic domain of MT1-MMP, a unique structural feature of the transmembrane MMPs, in regulation of enzyme function.

In spite of the many advances, we have only seen a glimpse of the MMP world. There is much more ahead to be known about this fascinating group of proteases. Through it we may began to comprehend some of the mysteries of life as we perceive it. This understanding will lead to the growth of scientific knowledge and the well-being of humanity. I wholeheartedly thank the contributors for their enlightening and scholarly reviews. A special thanks to the

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